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Abstract: Antiangiogenic treatment has recently become an integral part of modern cancer therapy targeting the vasculature of numerous aggressive malignancies including glioblastoma. There is preclinical evidence that antiangiogenic therapies promote glioma cell invasiveness. In clinical series, upon progression on antiangiogenic therapy with the vascular endothelial growth factor-directed antibody bevacizumab (BEV), glioblastoma has been reported to display a more infiltrative pattern of recurrence. This distant spread at recurrence or progression and a gliomatosis cerebri-like growth pattern is best detectable on fluid-attenuated inversion recovery MRI. The frequency of up to 20% to 30% of such a pattern in BEV-treated patients is higher than expected to occur without BEV. Older reports and common clinical knowledge estimate the frequency of diffuse or distant spread in recurrent glioblastoma at 10%. This observation stimulated two streams of research. One is to overcome this often insidious adverse effect of antiangiogenic treatment, to optimize antiangiogenic therapies and to face this major challenge, integrating antiangiogenic with anti-invasive mechanisms into one combined treatment concept. The second is questioning a specific property of antiangiogenic therapy to induce diffuse or distant spread. Here, alternative hypotheses of increased awareness and better imaging as well as invasiveness being part of the natural course of the disease have been tested. Without doubt, migration and invasiveness are major obstacles to successful glioma therapy, notably local therapies, both in the natural course of the disease and in the concept of "evasive resistance." However, clinical analyses of case series, matched pairs analyses, and follow-up on the BRAIN trial (A Study to Evaluate Bevacizumab Alone or in Combination with Irinotecan for Treatment of Glioblastoma Multiforme), which led to accelerated approval of BEV for recurrent glioblastoma in the United States, have not supported a specific propensity of BEV to induce diffuse growth or distant spread at recurrence.

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Patterns of Progression in Malignant Glioma Following Anti-VEGF Therapy: Perceptions and Evidence

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Abstract

Antiangiogenic treatment has recently become an integral part of modern cancer therapy targeting the vasculature of numerous aggressive malignancies including glioblastoma. There is preclinical evidence that antiangiogenic therapies promote glioma cell invasiveness.

In clinical series, upon progression on antiangiogenic therapy with the VEGF-directed antibody bevacizumab (BEV), glioblastoma have been reported to display a more infiltrative pattern of recurrence. This distant spread at recurrence or progression and a gliomatosis cerebri-like growth pattern is best detectable on fluid attention inverse recovery (FLAIR) magnetic resonance images (MRI). The frequency of up to 20-30% of such a pattern in BEV-treated patients is higher than expected to occur without BEV. Older reports and common clinical knowledge estimate the frequency of diffuse or distant spread in recurrent glioblastoma at 10%.

This observation stimulated two streams of research. One is to overcome this often insidious adverse effect of anti-angiogenic treatment, to optimize antiangiogenic therapies and to face this major challenge, integrating antiangiogenic with antiinvasive mechanisms into one combined treatment concept. The second is questioning a specific property of antiangiogenic therapy to induce diffuse or distant spread. Here, alternative hypotheses of increased awareness and better imaging as well as invasiveness being part of the natural course of the disease have been tested.

Without doubt, migration and invasiveness are major obstacles to successful glioma therapy, notably local therapies, both in the natural course of the disease and in the concept of „evasive resistance“. However, clinical analyses of case series, matched pairs analyses and follow up on the BRAIN trial, which led to accelerated approval of BEV for recurrent glioblastoma in the United States, have not supported a specific propensity of BEV to induce diffuse growth or distant spread at recurrence.

Abbreviations

Apparent diffusion coefficient (ADC), Bevacizumab (BEV), diffusion-weighted image (DWI), European Organization for Research and Treatment of Cancer (EORTC), Food and Drug Administration of the USA (FDA), European Medical Agency (EMA), fluid-attenuated inversion recovery (FLAIR), magnetic resonance imaging (MRI), National Cancer Institute of Canada (NCIC), progression-free survival (PFS), response assessment in Neurooncology (RANO) working group criteria, response rate (RR), T1-weighted MRI post contrast (T1+c), temozolomide (TMZ), vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR)

Introduction

The vascular endothelial growth factor (VEGF) antibody bevacizumab (BEV) has increased the repertoire of medical treatment options for patients with recurrent glioblastoma. Two uncontrolled phase II studies [1,2] were the basis for approval in the USA in May 2009 whereas the European Medial Agency (EMA) rejected approval in the EU [3]. In the US the rate of objective responses (RR) [4] was accepted as a denominator for clinical relevance posing increasing weight on magnetic resonance imaging (MRI) as a surrogate marker for treatment efficacy. Anti-VEGF/VEGF receptor (VEGFR) compounds [5] at least as part of their mode of action induce normalization of the vasculature [6] by inhibiting pathological proliferation of endothelial cells and immature vessel formation. Secondly, as early as 1-2 days after initiation of therapy, a reduction of the permeability of the blood-brain-barrier results in decreased contrast enhancement and edema and high objective radiological response rates of 25-60% [1,2,5,7,8]. The makeup of the current as well as novel revised response criteria do not allow to easily differentiate this effect on the barrier permeability from a direct antitumor effect [9,10]. So far, the unprecedented high response rates these agents produced in recurrent glioblastoma have not translated into a survival benefit of the same magnitude [11].

Accumulating evidence incriminates therapeutically active antiangiogenic therapies to elicit an adaptive-evasive response involving augmented tumor cell invasion or increased dissemination and distant metastasis in various neoplasias both inside and outside the central nervous system (CNS) [12,13]. Preclinical studies have indicated that anti-VEGF therapy may increase the tendency of tumor cells to invade by co-opting existing blood vessels [14,15]. For the molecular mechanisms involved two major hypotheses are discussed. Antiangiogenic therapy increases hypoxia and acidosis, which activates survival signals, like the *mammalian target of rapamycin (mTOR)/protein inositol 3-kinase pathway*, and promotes glycolytic energy metabolism and autophagy [16]. Alternatively or in addition, antiangiogenic therapy with targeted

agents like antiangiogenic radiotherapy [17,18] induces specifically, and as an undesirable side effect, cell motility.

For BEV, various patient series have suggested an increase in diffusely or distantly recurring tumors [11,19]. This gliomatosis-like phenotype or remote spread is best depicted on fluid-attenuated inversion recovery (FLAIR) MRI sequences [11]. Determination of the extent of this non-enhancing component of the tumor on the T2-weighted and FLAIR image sequences is difficult because of the similar appearance of peritumoral edema, which also has a bright signal on T2-weighted or FLAIR MRI sequences.

It may happen that despite persistent reduction in contrast enhancement an increase in non-enhancing T2 or FLAIR signal alterations suggestive of infiltrative tumor develops [11,19,20]. This dissociation is called “discordance” between the information gathered on T1+c and T2 images [20,21]. Amongst others this led to a reconsideration of the Macdonald criteria [9]. The response assessment criteria developed by the Response Criteria in Neurooncology Working Group (RANO) will qualitatively consider enlarging areas of non-enhancing tumor as evidence of tumor progression [10].

Here, the question whether anti-angiogenic treatments really enhance distant tumor spread compared with classical salvage regimens or the natural course of the disease is discussed based on the review of existing literature. To approach the topic of recurrence pattern analysis in glioma in the future, relevant preclinical paradigms have to be developed and working criteria for future assessment of recurrence patterns in the clinic need to be discussed.

Methods

Principles

To assess the impact of anti-VEGF/VEGFR treatments on the recurrence pattern in glioma, consecutive MRI (before, during and after treatment) have to be analyzed in T1-weighted sequences with contrast, T2-weighted or FLAIR sequences and possibly also diffusion-weighted images at certain, fixed intervals. Lack of stringent MRI follow-up makes the comparison between different reports on recurrence patterns very difficult. This can be done on a case-by-case basis or group-wise. Also, uncontrolled series or controlled studies at different levels of control (matched pairs or randomized trial) can be used.

Analysis of tumor location

A group-wise analysis has been developed for the analysis of the recurrence pattern of glioblastoma patients treated within the EORTC 26981/22981/NCIC CE.3 registration trial for temozolomide. Briefly, mapping of lesions is performed by the experimenters without knowledge of the clinical features of the patients. The boundary of the tumor location at baseline and at follow-up is delineated using MRIcro software [22] or exported from the 3D-raw MRI data and mapped on the template MRI from the Montreal Neurological Institute (www.bic.mni.mcgill.ca/cgi/icbm_view) that is distributed with freely available software, MRIcro. The template scan provides various anatomical landmarks for precisely plotting the localization of the tumor if import of data is not feasible. Lesions are mapped onto the slices that correspond to the MNI z-coordinates using the identical or the closest matching transversal slices of each individual. Tumors are mapped for each individual, with separate tumor maps generated for the baseline and recurrence scan. The logic of the analysis is straightforward. First, tumor lesions for a patient group at baseline and lesions for this group at recurrence are defined on the same template image. Next, the lesions at baseline are added together, creating an overlap image showing the regions of involvement. The same is carried out for the

lesions at recurrence. Finally, the overlap image of the lesions at recurrence are subtracted from the lesion overlap image at baseline. This method creates an image that shows regions that are commonly damaged in the patient group at recurrence but are typically spared in this group at baseline (coded as positive values), regions specifically damaged at baseline (coded as negative values) and regions that are damaged/spared in equal proportions between the two stages (values near zero) [23].

Criteria for the case-by-case analysis

Although the group-wise analysis is an elegant measure analyzing a cohort rather than individual patients, it suffers from the mass effects of larger tumors on the normal anatomical structures. Hence, although interesting for the assessment of recurrence patterns in newly diagnosed glioblastoma [23], it may be less valuable in recurrent disease with a large tumor volume at baseline. Therefore, it may also be necessary to assess single patients. Criteria for the assessment are detailed in the Table.

Evidence of increased frequency of remote relapse with BEV treatment?

There is concern from earlier clinical observations that anti-angiogenic treatment may prevent the formation of a tumor bulk, but may not be effective against progression in the infiltrative zone. Infiltrative growth is held responsible for morbidity and survival [11,24] and diffusely infiltrative recurrence [25] may escape classical T1+c MRI response assessments. In clinical series, upon progression on antiangiogenic therapy with the BEV, glioblastomas often displayed a more infiltrative pattern of recurrence. Preclinical data suggest vascular co-option as an escape mechanism to anti-angiogenic treatments. This is challenged by the fact that the area infiltrated by these tumor satellites [8,14,26] may not exceed the area of the untreated control tumors. Further, treatment with anti-angiogenic agents nevertheless results in impressive effects on OS in animal models [8,15,27]. This allows the differential hypothesis of anti-angiogenic therapy failing at the tumor-vascular interface, probably because of altered physiological, metabolic conditions in close proximity to the vessel. Norden et al. [20] looked at 55 BEV-treated and 19 control patients. Although they did not demonstrate a difference in recurrence patterns between both groups, they concluded that there might occur a relevant discordance between the T1+c and the FLAIR appearance of the recurrent BEV-treated tumors. They observed an increase in the FLAIR lesions especially in patients, which had at least a minor response on T1+c MRI sequences. This fact has supported the notion that in the era of anti-angiogenic treatments, contrast enhancement may not reliably signify tumor response. There is thus a need to account for the non-enhancing component of the tumor to accurately assess the efficacy of novel therapeutic modalities [9]. Further, in their work there was no difference in the rate of distant recurrences dependent on the fact whether BEV was given as a monotherapy or in conjunction with a chemotherapy. Of note, so far all attempts to combine BEV at recurrence of a glioma with another cytotoxic regimen failed to show additional benefit over the published efficacy data from the BRAIN trial, that is, that obtained with BEV alone.

No shift of recurrence pattern in BEV versus BEV plus CPT-11 treated patients: an analysis from the BRAIN trial

The recurrence pattern analysis of the BRAIN trial was looking for a shift from local tumors to distant or diffuse recurrence when treated with BEV or BEV plus irinotecan. The analysis indicated that between 20-30% tumors recurred remotely. Further, a distant recurrence was not predictive for a poor outcome compared to patients with local recurrences [27]. Comparing BEV and BEV plus CPT-11 from the BRAIN trial,[1] there was even a larger shift in the recurrence pattern from local to distant or diffuse in the BEV+ irinotecan arm as compared to BEV alone [22]. This does not support the idea that additional chemotherapy may prevent the untoward switch of the tumor phenoptype to a more invasive growth pattern.

Distant or diffuse recurrence may be a feature of late-stage glioma rather than a specific property of antiangiogenic treatments

The clinical data looked at so far are not controlled, but either used historical comparisons or analyzed not the impact of BEV itself, but the differential effect of CPT-11 plus BEV *versus* BEV alone as in the BRAIN trial. Others challenge the systematics of an analysis by providing results (distant/diffuse or local) for each step of a patients' history with multiple recurrences, each with a risk of around 20% to be distant. Here, eventually each patient should suffer from a distant recurrence, arguing more for invasion belonging to the natural course of the disease rather than a specific phenomenon in anti-VEGF treated patients [28,29]. To determine the overall frequency of distant recurrences in BEV-treated patients as assessed by the outlined group-wise methodology [23], we analyzed MRI examinations of 112 patients prior to and at failure of BEV. The frequency of distant recurrences in this patient series was 23%. Of note, 20% distant recurrences had been found in an analysis of the recurrence patterns at

first progression of the non-BEV-containing EORTC 26981/22981/NCIC CE.3 trial [23] and prior data suggested a frequency of distant failure of between 20 and 30% with BEV [11,19,20]. Therefore, a controlled analysis should ask the question whether distant recurrences are more frequent in BEV-treated patients *versus* patients with similar clinical characteristics who have not been exposed to BEV or another anti-angiogenic treatment in the observation period.

In our set of patients analyzed, 20.5% (BEV) and 22.7% (non-BEV) had displayed distant recurrence according to the criteria (Table) at entrance to the recurrence pattern analysis performed to check for the BEV effect. In the study, distant or diffuse recurrences with the treatments of this analysis at recurrence were observed in 22% (10 of 44, BEV) and 18% (8 of 44, non-BEV) on T1+c and in 25% (11 of 44, BEV) and 18% (8 of 44, non-BEV) on FLAIR sequences. In that analysis, the risk of distant or diffuse recurrence in matched pairs did not differ between BEV-containing and BEV-free treatments [30]. These data in the BEV group and the methodology except for a lesser variance (< 2 cm instead of < 3 cm) in the definition of local recurrence and the addition of the group-wise analysis are consistent with the analysis of the BRAIN trial [1].

Translational imaging research in a controlled trial may provide a definite answer

A major concern with anti-angiogenic treatments for glioblastoma is the hypothesis that these treatments transform a pro-angiogenic into a pro-migratory phenotype, resulting in more diffusely infiltrating tumors and finally more neurological morbidity after an initial phase of symptom relieve [25]. The therapeutic need in recurrent glioblastoma is evident from the published overall survival data in that situation, ranging from 5 to 10 months. The role of BEV in brain tumors is not completely clear in the absence of phase III trials, neither is there proof for its superiority over any other cytotoxic treatment at recurrence. Even if considered efficacious the best data with BEV leave wide room for improvement and a systematic controlled evaluation of combinations

between BEV and cytotoxic agents is missing. Lomustine is used as control arm in ongoing phase II and III trials, but has limited efficacy in randomized phase III trials in the era with temozolomide in the first-line treatment [31]. This is true although in a recently completed phase III trial of the VEGFR-2 inhibitor cediranib, neither the drug nor the combination with lomustine was superior to lomustine alone, arguing against lomustine being an insufficient comparator for modern trial [32]. In addition, gliomatosis remains an undefined concern after BEV treatment. It may be a specific unwanted effect of BEV in some patients, but is also seen with conventional chemotherapy at recurrence. It will be interesting to clarify whether this is a specific class property of antiangiogenic agents or a phenomenon of later stage glioblastoma. Therefore, a careful assessment on how BEV and lomustine may contribute to the standard of care requires a careful well-built/ step-wise approach.

Conclusions

Norden et al. [20] did not demonstrate a difference in recurrence patterns between BEV- and non-BEV-treated patients, but concluded that there might occur a relevant discordance between T1+c and FLAIR appearance of the BEV-treated tumors. An increase in the FLAIR lesions especially in patients demonstrating at least a minor response in T1+c was observed and finally added to the recognition that especially in the era of anti-angiogenic treatments, a reduction of contrast enhancement may not reliably signify tumor response. There was thus a need to account for the non-enhancing component of the tumor to assist with the accurate assessment of the efficacy of novel therapeutic modalities. These data in addition to the debate around peudoresponse led in the set-up of a working group to initiate a discussion on the imaging criteria in glioma (RANO working group), which already published updated imaging criteria recognizing the problems discussed here.

Second, the available clinical analyses argue against the propensity of BEV to induce clinically meaningful and T1+c MRI-negative invasiveness as demonstrated by FLAIR images. Distant tumor spread may instead be a result of increased awareness or prolonged survival in glioblastoma patients.

Third, the relevance of diffusion weighted imaging (DWI) restrictions on MRI is unclear. They have been proposed as a novel pattern of progression under BEV treatment [23] In contrast, DWI restriction might also reflect an unusual response pattern [33]. DWI restriction occurred within the previously enhancing tumor volume and corresponded to atypical necrosis [34]. More unlikely, DWI restrictions may reflect vascular, ischemic complications of BEV treatment.

Last, this data needs to be confirmed and methodologically expanded in the upcoming randomized trials, e.g., by the EORTC with strong imaging translational research.

Papers of particular interest, published recently, have been highlighted as:
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•• Of major importance

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